

REMARKS

By the present communication, claim 15 has been amended; no claims have been canceled; and no claims have been added. The amendments do not constitute new matter and are fully supported by the specification and claims as filed. For example, support for the amendments to claim 15 may be found in Example 3 of the specification as filed, on page 50, lines 11-14. Thus, upon entry of the present amendment, claims 15, 19-23 and 37 will be pending in this application.

Objection to the Title

The Office Action alleges that the title is not indicative of the invention to which the claims are directed. Without acquiescing to the rationale of the Office, Applicants have amended the title to recite "[A]ntibodies directed to fragments of connective tissue growth factor (CTGF) polypeptide." As such, Applicants submit that the amended title is clearly indicative of the invention. Accordingly, Applicants respectfully request all objections to the title be withdrawn.

Rejections under 35 U.S.C. §112, Second Paragraph

Applicants respectfully traverse the rejection of claims 15, 19-23, and 37 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants' regard as the invention.

Specifically, the Office Action alleges that residues 4-74 of SEQ ID NO:4 do not constitute a C-terminal fragment of CTGF as recited in claim 15. Without acquiescing to the reasoning presented in the Office Action, and in order to expedite prosecution of the present application, Applicants have amended claim 15 by deleting recital of "C-terminal fragment" as well as deleting recital of amino acid residues 4 through 74 of SEQ ID NO:4.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §103(a)

Applicants respectfully traverse the rejection of claims 15, 19, 21-23 and 37 under 35 U.S.C. §103(a) as allegedly being obvious over Grotendorst et al. (the '040 patent).

The recent U.S. Supreme Court decision in the *KSR International v. Teleflex Inc.* (82 USPQ 2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

Specifically, the Office Action alleges that the '040 patent describes monoclonal or polyclonal antibodies which specifically bind to CTGF and not to PDGF (claims 2-4), and that antigenic fragments may be used to make the antibodies. Additionally, the Office Action alleges that the '040 patent also discloses at column 7 that "antibodies were made to synthetic peptides containing the carboxyl sequences of the PDGF protein...which antibodies bound to CTGF" (Office Action, page 3).

Without acquiescing to the reasoning presented in the Office Action, and to expedite prosecution of the present application, Applicants have amended the claims by deleting antibodies to amino acid residues 4 through 74 of SEQ ID NO: 4. Additionally, the claims have been amended to recite "wherein the antibody inhibits DNA synthesis but does not inhibit collagen synthesis". Accordingly, the amended claims are directed to an antibody that specifically binds to a fragment of connective tissue growth factor (CTGF) polypeptide, but not platelet derived growth factor (PDGF), wherein the antibody inhibits DNA synthesis but does not inhibit collagen synthesis, and wherein the fragment of CTGF consists of amino acid residues 75 through 172 of SEQ ID NO:4. The antibodies of the present claims do not cross react with

PDGF, but rather bind specifically to epitopes on polypeptide fragments corresponding to exon 5 of the C-terminus of CTGF. Examples 3 and 4 of the specification of the present application describe generation of antibodies specific to the C-terminus of the CTGF polypeptide which were unexpectedly found to regulate specific biological activities of CTGF (*e.g.* inhibition of DNA synthesis).

Applicants respectfully submit that the claimed invention is based on the discovery that particular fragments of CTGF have particular biological activities. The N-terminus and C-terminus of CTGF have different biological activities. The N-terminal portion of CTGF stimulates extracellular matrix and collagen synthesis while the C-terminal portion promotes DNA synthesis. Such activities are not assigned to specific regions of CTGF in the '040 patent. The Office Action alleges that the claim limitation requiring that the claimed antibodies inhibit DNA replication is inherent to the claimed antibodies. As such, the Office Action alleges that "when one combines the teaching of using antibodies that inhibit the mitogenic ability of CTGF, which would also inhibit DNA synthesis, antibodies that have that property" would be obvious in view of the '040 patent (page 4, lines 18-21 of the Office Action). Without acquiescing to the rationale provided in the Office Action, and in order to expedite prosecution of the instant application, Applicants have amended the claim to recite that the claimed antibody inhibits DNA synthesis but does not inhibit collagen synthesis as taught in Examples 3 and 4 of the specification. Accordingly, without such teachings, the present invention would not have been obvious to one of skill in the art because there was no motivation to generate antibodies specifically to polypeptide fragments of the C-terminus of CTGF encoded by polynucleotide sequences that include exon 5 to achieve inhibition of a specific biological activity.

For the aforementioned reasons, Applicants respectfully submit that the '040 patent fails to render obvious the presently claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 15, 19, 21-23 and 37 under 35 U.S.C. §103(a).

Applicants respectfully traverse the rejection of claim 20 under 35 U.S.C. §103(a) as allegedly being obvious over Grotendorst et al. (the '040 patent), in view of Hoogenboom et al. (U.S. Patent No. 5,565,332). In addition to the alleged teachings of the '040 patent recited above, the Office Action further alleges that Hoogenboom et al. teaches human and humanized antibodies and that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the anti-CTGF antibodies of the '040 patent into the human or humanized antibodies described in Hoogenboom et al.

For the reasons previously presented above, Applicants submit that the '040 patent does not render obvious the presently claimed invention. Additionally, Applicants respectfully submit that even if one were to combine the '040 patent with Hoogenboom et al., the resulting combination would not result in the claimed anti-CTGF antibodies that bind specifically to epitopes on polypeptide fragments corresponding to exon 5 of the C-terminus of CTGF. Applicants' invention is directed to antibodies that specifically bind epitopes on polypeptide fragments of the C-terminus of CTGF corresponding with exon 5, and not PDGF, wherein the antibody inhibits DNA synthesis but does not inhibit collagen synthesis, and wherein the fragment of CTGF consists of amino acid residues 75 through 172 of SEQ ID NO:4. Applicants submit that because the '040 patent fails to specifically teach anti-CTGF antibodies that bind specifically to epitopes on polypeptide fragments corresponding to exon 5 of the C-terminus of CTGF, or even a specific biological activity associated with exon 5, the additional teachings of Hoogenboom et al. generally describing humanized antibodies still does not provide humanized anti-CTGF as claimed. The '040 patent alone or combination with the teachings of Hoogenboom et al. fails to teach the claimed antibodies.

Applicants respectfully submit that neither the '040 patent nor Hoogenboom et al. provide any motivation to obtain an anti-CTGF antibody that binds specifically to epitopes on polypeptide fragments corresponding to exon 5 of the C-terminus of CTGF. Since the N-terminus and C-terminus of CTGF have different biological activities that were not previously

assigned to specific regions of CTGF at the time of the '040 patent, there was no motivation to generate antibodies to the regions of CTGF polypeptide as disclosed in the present application and currently claimed. Accordingly, because the cited references fail to disclose the biological activities of the N-terminal and C-terminal fragments of CTGF, the present invention is not rendered obvious because there was no motivation or teachings to generate antibodies specifically to fragments of the C-terminus of CTGF encoded by a polynucleotide sequence including exon 5 of CTGF as presently claimed.

Accordingly, Applicants submit that a *prima facie* case of obviousness has not been established and withdrawal of the rejection is respectfully requested.

Double patenting rejection

Claims 15, 19, 21-23 and 37 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 2-4 of Grotendorst et al. (the '040 patent). Additionally, claim 20 is rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 2-4 of Grotendorst et al. (the '040 patent) in view of Hoogenboom et al. (U.S. Patent No. 5,565,332). Applicants respectfully traverse the rejections as they apply to the pending claims.

For the reasons presented above, Applicants submit that the claimed invention is non-obvious in view of the '040 patent the alone or in combination with Hoogenboom et al.. As stated above, Applicants submit that it would not have been obvious to generate anti-CTGF antibodies directed to epitopes on CTGF polypeptide fragments corresponding to exon 5 of the C-terminus of CTGF because no particular biological activity had been assigned to either the N-terminal or C-terminal fragments in the '040 patent. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 15, 19, 21-23 and 37.

In re Application of:
Grotendorst and Neff
Application No.: 10/658,856
Filed: September 9, 2003
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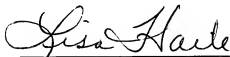
PATENT
Atty Docket No.: FIBRO1130-3

Conclusion

In summary, for the reasons set forth herein, Applicants submit that the claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge the total amount of \$65.00 for the One-Month Extension of Time fee, small entity, to Deposit Account No. 07-1896. No other fees are deemed necessary with the filing of this paper. However, the Commissioner is further authorized to charge any additional fees, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number.

Respectfully submitted,



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